Clinical Pharmacology in Drug Development

Population Pharmacokinetic Modeling and Probability of Target Attainment Analyses in Asian Patients With Community-Acquired Pneumonia Treated With Ceftaroline Fosamil

Journal:	*Clinical Pharmacology in Drug Development*
Manuscript ID	CPD-18-0057.R2
Manuscript Type:	Original Manuscript
Date Submitted by the Author:	n/a
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Keywords:	Ceftaroline fosamil, community-acquired pneumonia, population pharmacokinetics, probability of target attainment, PK/PD
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Population Pharmacokinetic Modeling and Probability of Target Attainment Analyses in Asian Patients With Community-Acquired Pneumonia Treated With Ceftaroline Fosamil

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Running title: Ceftaroline fosamil Asia CAP PTA analysis

Key words: Ceftaroline fosamil, community-acquired pneumonia, population pharmacokinetics, probability of target attainment, PK/PD

Word count: 5114 (max 6500)

Tables/Figures: 8 (max 8)

References: 35 (max 150)

Acknowledgments

The authors would like to thank all the subjects and investigators involved in the trials included in this population PK analysis. The phase 3 Asia CAP study and the phase 1 Chinese PK study were originally sponsored by AstraZeneca and are now sponsored by Pfizer. All other studies included in the population PK analysis were sponsored by Allergan. AstraZeneca's rights to ceftaroline fosamil were acquired by Pfizer in December 2016. The authors would like to thank Pharmetheus (Uppsala, Sweden), which received financial support from AstraZeneca in connection with developing the population PK model used in this analysis.

D.Z. and N.A-H. are employees of and shareholders in AstraZeneca. J.L. and S.D. are former employees of and shareholders in AstraZeneca. All authors were involved in the analysis concept and design, interpreting the data, and developing the manuscript, and reviewed and approved the final version of the manuscript for submission. Medical writing support was provided by Sirisha Bulusu, MBiochem, at Prime, Knutsford, Cheshire, UK, and was funded by AstraZeneca and Pfizer.

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Abstract

Efficacy of ceftaroline fosamil, the prodrug of the active metabolite ceftaroline, was demonstrated in a phase 3 study of hospitalized Asian patients with Pneumonia Outcomes Research Team (PORT) risk class III-IV community-acquired pneumonia (CAP) (NCT01371838). The objectives of the current analysis were to expand an existing ceftaroline and ceftaroline fosamil population pharmacokinetic (PK) model with data from this phase 3 study and a phase 1 study (NCT01458743) assessing ceftaroline PK in Chinese healthy volunteers, and to evaluate probability of PK/pharmacodynamic (PK/PD) target attainment (PTA) in Asian patients with CAP treated with ceftaroline fosamil. Ceftaroline plasma concentration-time courses were simulated for 5000 Asian patients with CAP for different renal function subgroups using the final model. PTAs were calculated for *Streptococcus pneumoniae*, *Staphylococcus aureus* and non–extended-spectrum β-lactamase-producing *Enterobacteriaceae*. PTAs were also evaluated at ceftaroline MIC_{90} values of isolates collected from Asia-Pacific surveillance studies (2012-2014), and at EUCAST and FDA/CLSI ceftaroline susceptibility breakpoints. The final model reasonably described the ceftaroline PK. Race was found not to be a significant covariate impacting ceftaroline PK, suggesting similar ceftaroline PK in Asian and Western populations when corrected for body weight. High PTAs (90-100%) were predicted for Asian patients with CAP treated with ceftaroline fosamil, covering MIC_{90} values of target CAP pathogens from the region. Similarly, >90% PTAs were predicted at EUCAST and FDA/CLSI clinical breakpoints for these pathogens. These results support use of the ceftaroline fosamil dosing regimens approved in Europe and the United States in Asian patients with PORT III-IV CAP.

Word count: 247 (max 250)

Introduction

Community-acquired pneumonia (CAP) causes significant morbidity and mortality worldwide and is associated with a substantial clinical and economic burden in the Asia-Pacific region.[1] Ceftaroline, the active metabolite of the prodrug ceftaroline fosamil, is a cephalosporin with *in vitro* activity against many of the major bacterial pathogens causing CAP, including the Gram-positive cocci such as *Streptococcus pneumoniae* and *Staphylococcus aureus*, and non–extended-spectrum β-lactamase (ESBL) producing Gram-negative bacteria such as *Haemophilus influenzae, Escherichia coli*, and *Klebsiella pneumoniae.*

The efficacy and safety of ceftaroline fosamil for the treatment of CAP has been assessed in 3 phase 3 studies. The FOCUS 1 and 2 studies (NCT00621504 and NCT0050910) included predominantly European and North American patients and demonstrated the noninferiority of ceftaroline fosamil 600 mg every 12 hours (q12h) versus ceftriaxone 1 g every 24 hours (q24h) in patients hospitalized with Pneumonia Outcomes Research Team (PORT) risk class III or IV CAP.[2,3] Subsequently, a phase 3 study (NCT01371838) in Asian patients hospitalized with PORT III-IV CAP demonstrated the superiority of ceftaroline fosamil 600 mg q12h versus ceftriaxone 2 g q24h.[4] A meta-analysis of these 3 studies demonstrated there was no evidence of heterogeneity between the studies, with clinical cure rates in each trial consistently favoring ceftaroline fosamil versus ceftriaxone.[5] Ceftaroline fosamil 600 mg q12h as a 1-hour IV infusion is approved in Europe for the treatment of adult and adolescent patients with CAP or complicated skin and soft tissue infections (cSSTI), and is also approved for similar indications in the United States and multiple other countries. Due to the predominantly renal excretion of ceftaroline, dosage adjustments are required for patients with creatinine clearance (CrCL) ≤50 mL/min.[6]

The pharmacokinetic (PK) profile of ceftaroline has been well-characterized in several phase 1 studies.[6] Following intravenous (IV) administration, the prodrug ceftaroline fosamil is rapidly converted into the active metabolite ceftaroline by plasma phosphatases.[6] Concentrations of the prodrug are measurable in plasma primarily during IV infusion and are typically not quantifiable beyond one hour following the end of IV infusion.[6,7] After conversion to ceftaroline, a small fraction is converted into an inactive metabolite, ceftaroline-M-1.[6] The primary route of elimination for ceftaroline fosamil and its metabolites is by renal clearance; between 40-70% of the ceftaroline fosamil dose is excreted in the urine as ceftaroline.[6] Ceftaroline exposures increase in a dose-proportional manner within the single dose range of 50 to 1000 mg and the mean terminal elimination half-life of ceftaroline in healthy adults is approximately 2.5 hours.[6] No clinical studies have assessed drug-drug interactions for ceftaroline fosamil, however as ceftaroline is not a substrate, inhibitor or inducer of major hepatic CYP450 enzymes in vitro, the overall drug-drug interaction potential is considered low.[6]

PK modelling and simulation play an important role in guiding the selection and validation of antibiotic dosage regimens.[8,9] PK data obtained for the antibiotic in the patient population of interest are used to develop population PK models which describe the concentration–time course of the antibiotic and characterize the effect of subject characteristics (covariates) on the PK parameters, while also accounting for random variability in concentrations within the patient population.[8,9] Using model parameters including variability, antibiotic concentration-time courses are simulated for a large patient populations receiving the intended dosage regimen (Monte Carlo simulations). These simulations can be used to determine the proportion of patients that achieve a pre-specified PK/PD target associated with antibiotic efficacy (typically derived from preclinical studies) and thus the probability of target attainment (PTA). The PTA values achieved across the antibiotic minimum inhibitory concentration (MIC) distributions of target pathogens can be used to inform dosing decisions.

A population PK model for ceftaroline and ceftaroline fosamil was initially developed based on adult PK data from healthy volunteers and phase 2 and 3 studies in patients with cSSTI[10] and subsequently updated to include data for patients with CAP from the FOCUS studies (unpublished data); a separate population PK model was also subsequently developed which included data from clinical trials in pediatric patients.[11] The clinical studies on which the original model was based primarily enrolled patients from Western countries. Two trials of ceftaroline fosamil have now been completed in Asian patients: the phase 3 Asia CAP study, and a phase 1 study in Chinese healthy volunteers (NCT01458743), which found broadly similar ceftaroline PK in healthy Chinese and Western subjects receiving equivalent twice- and three-times daily dosage regimens.[12] The objectives of the current analysis were to extend the previous ceftaroline and ceftaroline fosamil population PK model with PK data from these Asian studies, and to use the updated model to evaluate the PTA against key CAP pathogens in simulated Asian patients with CAP treated with ceftaroline fosamil.

Methods

Model Dataset

All studies included in the population PK model were performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and that were consistent with the International Conference on Harmonization. The clinical study protocols, informed consent form(s), and all other appropriate study-related documents were reviewed and approved by local independent ethics committees / institutional review boards. A summary of all the studies included in this analysis is presented in Supplementary Table 1.

A previously developed population PK model for ceftaroline and ceftaroline fosamil was used as the starting point to develop the model for this analysis. The dataset for the original model comprised patient PK data from 16 clinical studies of ceftaroline fosamil (11 phase 1, 1 phase 2, and 4 phase 3) that included healthy volunteers and patients with CAP or cSSTI (Supplementary Table 1).[2,3,6,13-19] Ceftaroline fosamil was given as an IV infusion in these studies, except for one study where ceftaroline fosamil was intramuscularly administered. These studies were termed the Western dataset, although a small proportion of Asian patients were also included.

To develop the final model, the Western dataset was pooled with data from the phase 3 Asia CAP study[4] and the phase 1 study in Chinese healthy volunteers.[12] The Asia CAP study included 771 Asian patients with PORT III-IV CAP from study centers in China, India, South Korea, Taiwan, and Vietnam who were randomized 1:1 to receive either ceftaroline fosamil 600 mg q12h (adjusted to 400 mg q12h in patients with moderate renal impairment [CrCL >30-50 mL/min]) or ceftriaxone 2 g q24h. Data for PK analysis were obtained from sparse plasma sampling (maximum of 4 samples per patient) in 86 Asian patients with CAP treated with ceftaroline fosamil in this study. Blood samples for PK analysis were obtained at the following times on day 3: within 15 minutes prior to the start of infusion 1, within 5 minutes following the end of infusion 2, between 1 and 3 hours after the end of infusion 2, and between 4 and 8 hours after the end of infusion 2. In total, there were 333 observed ceftaroline concentrations from these 86 patients. The phase 1 study included 26 Chinese subjects from a single study center in Beijing who received either a single 1-hour infusion of 600 mg ceftaroline fosamil on day 1 and day 8, and 1-hour infusions of ceftaroline fosamil 600 mg q12h on days 3 to 7 or a 2-hour infusion of 600 mg ceftaroline fosamil on day 1 and day 8, and 2-hour infusions of ceftaroline fosamil 600 mg every 8 hours (q8h) on days 2 to 7. PK data were obtained from intensive plasma concentration sampling throughout the study in all 26 subjects. Blood samples for PK analysis were obtained on days 1 and 8 at predose and at predefined intervals up to 48 hours after the start of infusion. A total of 740 observed ceftaroline concentrations were obtained from all 26 subjects.

Bioanalytical methods

Validated liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) methods were used to measure plasma concentrations of ceftaroline and ceftaroline fosamil in each study, apart from one study in which a validated high pressure liquid chromatography method with ultraviolet detection method was used (see Supplementary material for further details).[10] Lower limit of quantification (LLOQ) values for each study are summarized in Supplementary Table 1. Ceftaroline and ceftaroline fosamil concentrations reported as missing or below the LLOQ were expressed as missing for subjects/patients with dense PK sampling.

Model Development

The population PK model for ceftaroline and ceftaroline fosamil in the current analysis was developed using NONMEM™ version 7.2.0 and the stepwise covariate model building procedure in Perl-speaks-NONMEM. Estimation of population PK parameters was performed using the first-order conditional estimation method with interaction (FOCE-I).

The previous population PK model of ceftaroline and ceftaroline fosamil based on the Western dataset was described by a two-compartment disposition model for ceftaroline fosamil with an absorption compartment for intra-muscular dose administration and a two-compartment disposition model for ceftaroline assuming a complete conversion of ceftaroline fosamil to ceftaroline. Age, end-stage renal disease (ESRD) in nondialysis subjects, participant status (ie, with infection or healthy volunteers), and body surface area-normalized creatinine clearance (NCrCL; calculated using the Cockcroft-Gault method) were identified as significant covariates impacting the clearance (CL) of ceftaroline, and patients versus healthy volunteers was identified as a significant covariate impacting the central volume of distribution (V_c) of ceftaroline.

The previous model was adapted by fixing the ceftaroline fosamil PK parameters and excluding the ceftaroline fosamil concentrations to ensure numerical stability of the modeling computation, and by incorporating standard allometric models of body weight on CL and V_c parameters of ceftaroline fosamil and ceftaroline. The adapted model was used to re-evaluate the significance of the previously identified significant covariates using the pooled Western and Asian dataset by a stepwise backward elimination procedure.

To develop the final model, the effect of the race covariate (ethnicity defined by Caucasian, Black, Asian, and Other) on ceftaroline CL and V_c was evaluated using a forward selection and a backward elimination procedure for the pooled dataset (*P* value set to .001 for both the forward and backward selection). Conditional weighted residuals (CWRES; calculated as the FOCE approximated difference between an individual's data and the model prediction of that data divided by the root of the covariance of the data given the model)[20] with values >4 were removed in an iterative procedure to avoid undue influence of outlier values in the model.

Model Evaluation

Standard goodness of fit model diagnostic plots and the OFV provided by NONMEM were used during model development to evaluate the fit of the models to the data. The following model diagnostic plots were used: observed ceftaroline concentrations versus individual predictions (IPRED) or population predictions (PRED), individual weighted residual (IWRES) versus IPRED, and CWRES versus PRED. In addition, prediction-corrected visual predictive checks (pcVPC) with 95% confidence intervals were used to evaluate the predictive performance of the models. As the study design and covariates included in the model differed widely among studies and study arms, pcVPC was used instead of the traditional VPC approach.[21] In pcVPC, the observed and the simulated dependent variables are normalized based on the typical population prediction, which facilitates the evaluation of models based on data with a wide range in the dependent variables. For the pcVPCs, 1000 datasets were simulated using the doses and covariate data from the subjects that were used in the analysis dataset with the same study design. The observed and simulated ceftaroline concentration versus time profiles were compared graphically.

In this analysis, the ceftaroline fosamil PK parameters were fixed and the ceftaroline fosamil observations were therefore excluded in the development of the final model. The ability of the final model to predict the ceftaroline observations when the ceftaroline fosamil observations were excluded was evaluated by reintroducing the ceftaroline fosamil concentrations into the final model and performing similar model diagnostic plots and pcVPC plots to those described above.

Exposure Indices

Individual empirical Bayes estimates of PK parameters were used to predict individual ceftaroline exposure indices for area under the concentration-time curve at steady-state (AUC_{ss}) and maximum concentration at steady state ($C_{max,ss}$) and to derive an individual secondary ceftaroline parameter (terminal half-life of ceftaroline [$T_{1/2}$]). Exposure indices were calculated for 4 groups of Asian subjects at steady-state according to the ceftaroline fosamil dosage regimens administered in the phase 1 study in Chinese healthy volunteers and the phase 3 Asia CAP study: phase 1 subjects receiving 600 mg q12h 1-hour infusions, phase 1 subjects receiving 600 mg q8h 2-hour infusions, phase 3 patients receiving 600 mg q12h 1-hour infusions, and phase 3 patients receiving 400 mg q12h 1-hour infusions.

Monte Carlo Simulations

Monte Carlo simulation generates a set of PK parameter values for each simulated patient by random sampling within the predefined PK parameter distribution from the population PK model.[8] Ceftaroline concentration-time courses were simulated in 5000 Asian patients with CAP using the final population PK model. Individual patient PK parameters were simulated from the population model mean PK parameters, associated individual covariates from the covariate distribution, and inter-subject variability from the final model. To simulate individual patient covariates, random samples of age, body weight, body surface area (BSA), and CrCL were drawn from the multivariate normal distribution of these covariates at baseline in the 771 Asian patients from the Asia CAP study. The NCrCL was calculated as CrCL*1.73/BSA. In addition, 5000 covariate datasets were constructed for each of 3 subgroups based on subjects' renal function: normal (CrCL >80 mL/min), mild impairment (CrCL >50-80 mL/min), or moderate impairment (CrCL >30-50 mL/min).

PK/PD Targets

In similarity to other β-lactam antibiotics, the PK/PD index associated with *in vitro* and *in vivo* efficacy for ceftaroline is the percentage of time during the dosing interval that free drug plasma concentrations exceed the minimum inhibitory concentration of the bacteria (%*f*T>MIC).[22,23] PK/PD targets are the PK/PD index values for which the desired level of antibiotic efficacy is achieved (e.g. stasis, 1-$\log_{10}$ reduction or 2-$\log_{10}$ reduction in bacterial density of the infecting pathogen). Ceftaroline PK/PD targets for *S. pneumoniae* and *Enterobacteriaceae* were derived from a neutropenic murine thigh and lung infection model.[23] Median (range) %*f*T>MIC targets for *S. pneumoniae* were 35% (29-52%) for stasis, 44% (33-59%) for 1-$\log_{10}$ reduction, and 51% (36-64%) for 2-$\log_{10}$ reduction; for *Enterobacteriaceae*, median (range) %*f*T>MIC targets were 48.5% for stasis and 73% (39-89%) for 1-$\log_{10}$ reduction.[23] PK/PD targets for *S. aureus* were derived from 3 preclinical studies[23-25] and the mean %*f*T>MIC targets from these studies were used in this analysis: 27% for stasis, 31% for 1-log_{10} reduction, and 35% for 2-log_{10} reduction.[26] For non–species-specific PK/PD targets, targets of 20-80% *f*T>MIC with 10% increments were used.

The simulated steady-state ceftaroline plasma concentration-time courses were used to obtain the %*f*T>MIC for each patient during the dosing interval. A free fraction of 80% was applied for the ceftaroline plasma concentrations used for %*f*T>MIC calculations.

PTA Simulations

PTAs were calculated as the percentage of 5000 simulated patients in each renal function subgroup at steady state who met the species-specific or non–species-specific PK/PD targets described above for a range of MICs following administration of the approved ceftaroline fosamil dosing regimens for each subgroup: 600 mg as a 1-hour IV infusion q12h for subjects with normal renal function or mild renal impairment, and 400 mg as a 1-hour IV infusion q12h for subjects with moderate renal impairment.

Achievement of >90% PTA was used to evaluate the appropriateness of the ceftaroline fosamil dosage regimen at a given MIC value. PTAs were calculated for MIC values of 0.125, 0.5, 1, 2, 4, and 8 mg/L. The PTAs at the highest ceftaroline MIC values of isolates collected from the Asia CAP study[4] and the MIC_{90} values (MIC required to inhibit 90% of isolates) of clinical isolates obtained from recent Asia-Pacific antibiotic susceptibility surveillance studies were determined. MIC_{90} values were recorded for clinical isolates of *S. pneumoniae* (penicillin-susceptible, penicillin-intermediate, and penicillin-resistant), *S. aureus* (methicillin-sensitive and methicillin-resistant; MSSA and MRSA), *E. coli* and *K. pneumoniae* collected in the Asia-Pacific region during 2012, 2013, and 2014 as part of the AWARE ceftaroline surveillance program.[27,28] In the 2013 and 2014 surveillance studies, a ceftazidime or aztreonam MIC of >1 mg/L was used as a phenotypic marker to define ESBL-positive *Enterobacteriaceae* isolates.[29] The PTA by MIC curves for each PK/PD target and ceftaroline MIC frequency distributions from the 2014 Asia-Pacific surveillance study were co-plotted for visual examination of appropriate PTA coverage for *S. pneumoniae* (penicillin-susceptible, penicillin-intermediate, and penicillin-resistant). The PTA was also calculated at the ceftaroline EUCAST and FDA/CLSI clinical susceptibility MIC breakpoints established for the q12h dosage regimens against *S. pneumoniae, S. aureus, Enterobacteriaceae, H. influenzae* and the EUCAST non–species-specific breakpoint (summarized in Table 5).

Results

Final Population PK Model

Baseline covariates included in the Western, Asian, and pooled Western and Asian analysis datasets for the final model are summarized in Supplementary Table 2. The pooled Western and Asian dataset for the final model comprised 533 subjects (348 male,185 female) with a median age of 47 years (range 12-93 years) and a median body weight of 72 kg (range 40-134 kg). Of these, 221 (41%) were healthy volunteers and 312 (59%) were patients with cSSTI or CAP; overall 123 (23%) subjects were of Asian ethnicity. In total, 320 (60%) subjects in the pooled Western and Asian dataset had normal renal function, 146 (27%) had mild renal impairment, 52 (10%) had moderate renal impairment, 9 (2%) had severe renal impairment, and 6 (1%) had ESRD or were on dialysis.

Based on the original Western dataset model, ceftaroline and ceftaroline fosamil concentration-time courses were both modeled as 2-compartment disposition PK models in the final model, with an assumption of 100% conversion of ceftaroline fosamil into ceftaroline and a first-order absorption of ceftaroline fosamil after intra-muscular administration of ceftaroline fosamil. With the impact of body weight on ceftaroline fosamil and ceftaroline CL and V_c fixed to an allometric model, all the previously identified significant covariates (age, NCrCL, ESRD in nondialysis patients and patients versus healthy volunteers) were still statistically significant ($P < .001$), with the adapted model for the pooled dataset including the Western dataset, as well as data from the 2 new Asian studies. Race, including Asian ethnicity as a subgroup, was not a significant covariate impacting the CL and V_c of ceftaroline.

The final model described the observed ceftaroline concentrations well for all subjects in the pooled Western and Asian dataset, as shown by the typical goodness-of-fit diagnostic plots (Figure 1), and the pcVPC plots using the final model for all subjects (Figure 2) and for patients from the Asia CAP study (Figure S1). Thus, the final model was considered appropriate for calculating the PTA in Asian patients with CAP. In this analysis, population PK parameters for ceftaroline fosamil were fixed and ceftaroline fosamil concentrations were excluded in the development of the final model for ceftaroline. However, in a sensitivity analysis where ceftaroline fosamil concentrations were re-introduced into the final model, goodness-of-fit plots (Figure S2) and the pcVPC plot for ceftaroline (Figure S3) showed that the final model still provided a reasonable description of ceftaroline observations. This indicated that fixing the PK parameters for ceftaroline fosamil and excluding ceftaroline fosamil observations had little impact on the goodness-of-fit to the ceftaroline concentrations, and that the final ceftaroline model was therefore suitable for the subsequent PTA simulations. Parameter estimates (fixed) for ceftaroline and ceftaroline fosamil in the final model are summarized in Table 1. Individual predicted exposure indices (AUC_{ss} and $C_{max,ss}$) and $T_{1/2}$ by ceftaroline fosamil dosage regimen received in the phase 3 Asia CAP study and the phase 1 study in Chinese healthy volunteers are presented in Table 2.

PTA in Asian CAP Patient Population With Normal Renal Function

Streptococcus pneumoniae

PTAs for stasis (35% *f*T>MIC), 1-$\log_{10}$ kill (44% *f*T>MIC), and 2-$\log_{10}$ kill (51% *f*T>MIC) for *S. pneumoniae* were >97% for all PK/PD targets at ceftaroline MICs of 1 mg/L or lower (Table 3) for patients with normal renal function (CrCL >80 mL/min) receiving the ceftaroline fosamil 600 mg q12h dosing regimen. Ceftaroline MIC_{90}s against *S. pneumoniae* isolates collected from 2012, 2013, and 2014 Asia-Pacific surveillance studies ranged from 0.06 to 0.5 mg/L (2012), 0.12 to 0.5 mg/L (2013), and 0.12 to 1 mg/L (2014) for penicillin-susceptible (PSSP), penicillin-intermediate (PISP), and penicillin-resistant (PRSP) strains (Table 4). For all PK/PD targets, >97% PTAs were achieved for these MIC_{90} values (Table 4). A representative PTA by MIC plot for *S. pneumoniae* overlaid with the ceftaroline MIC distribution for *S. pneumoniae* isolates from the Asia-Pacific region obtained during the 2014 surveillance program is shown in Figure 3. This shows high PTA coverage for ceftaroline across the range of MIC values for real-life clinical isolates. Moreover, the highest ceftaroline MIC observed for *S. pneumoniae* isolates in the Asia CAP study was 0.25 mg/L.[4] This is within the range of MIC_{90} values observed in the Asia-Pacific surveillance studies in 2012-2014 (Table 4), indicating >97% PTAs can be achieved for all the PK/PD targets in Asian patients with CAP caused by *S. pneumoniae*. Across all targets, estimated PTAs for *S. pneumoniae* were ≥99.9% at the EUCAST and FDA/CLSI clinical susceptibility breakpoints (≤0.25 and ≤0.5 mg/L, respectively; Table 5).

Staphylococcus aureus

PTAs were greater than 98% for all *S. aureus* PK/PD targets (27% *f*T>MIC, 31% *f*T>MIC, and 35% *f*T>MIC for stasis, 1-$\log_{10}$ kill, and 2-$\log_{10}$ kill, respectively) at ceftaroline MICs of 2 mg/L or lower for patients receiving ceftaroline fosamil 600 mg q12h (Table 3). This was in close agreement with the ceftaroline MIC_{90} against *S. aureus* strains (MSSA plus MRSA) isolated in the Asia-Pacific region in the surveillance studies from 2012-2014 (Table 4). PTA of >98% was achieved for all PK/PD targets at this MIC_{90} value (Table 3). The maximum ceftaroline MIC against

S. aureus isolated from patients in the Asia CAP study was 0.5 mg/L,[4] at which 100% PTA was achieved for all PK/PD targets (Table 3). Estimated PTAs for *S. aureus* at the EUCAST and FDA/CLSI ceftaroline susceptibility breakpoint (≤1 mg/L) were 100% for all PK/PD targets (Table 5).

Enterobacteriaceae

PTAs for stasis (48.5% *f*T>MIC) and 1-$\log_{10}$ kill (73% *f*T>MIC) by MIC for *Enterobacteriaceae* for patients receiving ceftaroline fosamil 600 mg q12h are shown in Table 3, with a PTA of >90% for all MICs up to 0.5 mg/L estimated for a 1-$\log_{10}$ kill PK/PD target. In the 2013 and 2014 surveillance studies, ceftaroline MIC_{90} values ≤0.5 mg/L against ESBL-negative *E. coli* and *K. pneumoniae* were observed; >90% PTAs are predicted for the stasis and 1-$\log_{10}$ kill PK/PD targets for these MIC_{90} values (Tables 3 and 4). The maximum ceftaroline MIC observed for ESBL-negative *Enterobacteriaceae* in the Asia CAP study[4] was 0.5 mg/L. Similar to *S. pneumoniae and S. aureus*, estimated PTAs for ESBL-negative *Enterobacteriaceae* were all >90% at the EUCAST and FDA/CLSI clinical susceptibility breakpoint (≤0.5 mg/L, Table 5).

Non–Species-Specific PK/PD Targets

PTA analyses were also conducted for non–species-specific PK/PD targets ranging from 20% *f*T>MIC to 80% *f*T>MIC for patients receiving the 600 mg q12h dosing regimen (Table 6). For lower ceftaroline MIC values (0.125 mg/L and 0.25 mg/L), >95% PTAs were predicted for a PK/PD target as high as 80% *f*T>MIC (Supplementary Table 3). For moderate MIC values (1 mg/L and 2 mg/L), >90% PTAs were predicted for a PK/PD target of 40% *f*T>MIC (Table 6). PTAs <7% were predicted for ceftaroline at MICs of >2 mg/L and PK/PD targets ≥50% *f*T>MIC (Table

6). Greater than 90% PTA was predicted at the EUCAST non–species-specific PK/PD breakpoint of ≤0.5 mg/L with a non–species-specific PK/PD target of ≥70% *f*T>MIC (Table 5). Non–species-specific PK/PD targets were also used to interpret *H. influenzae* susceptibility MIC breakpoints; for the EUCAST breakpoint (MIC ≤0.03 mg/L) 100% PTAs were predicted at anon–species-specific PK/PD target of 100% *f*T>MIC and for the FDA/CLSI breakpoint (MIC ≤0.5 mg/L) >90% PTA was predicted for a non–species-specific target of ≥70% *f*T>MIC.

PTA in Asian CAP Patient Population With Mild or Moderate Renal Impairment

Similar PTA analyses to those conducted for patients with normal renal function receiving ceftaroline fosamil 600 mg q12h were carried out for Asian CAP patients with mild renal impairment (CrCL >50-80 mL/min) receiving ceftaroline fosamil 600 mg q12h and patients with moderate renal impairment (CrCL >30-50 mL/min) receiving ceftaroline fosamil 400 mg q12h. In patients with mild or moderate renal impairment, the predicted PTAs were similar or slightly higher than those for patients with normal renal function (Supplementary Table 4 compared with Table 3, and Supplementary Table 5 compared with Table 3).

Discussion

The phase 3 Asia CAP study demonstrated the superiority of ceftaroline fosamil 600 mg q12h over ceftriaxone 2 g q24h in Asian patients with PORT III-IV CAP.[4] These data along with data from a phase 1 study in Chinese healthy volunteers[12] were used to update an existing population PK model for ceftaroline and ceftaroline fosamil to characterize their population PK and evaluate PTA in a representative Asian patient population with CAP treated with ceftaroline fosamil. Compared with an earlier ceftaroline and ceftaroline fosamil population PK model that was primarily based on Western healthy volunteers and cSSTI patients,[10] the model used in this analysis included additional data from Phase III patients with CAP and substantially more data from Asian subjects treated with ceftaroline fosamil.

The final model described the observed ceftaroline concentrations well for all Western and Asian subjects in the dataset. Importantly, race, as defined by ethnicity, was not a statistically significant covariate impacting ceftaroline CL or V_c in the final model. This finding suggests that the PK characteristics of ceftaroline are similar in the Asian and Western populations, when corrected for body weight. Individual predicted ceftaroline exposures for Asian subjects derived from the final model were similar to those reported for noncompartmental analyses in both Chinese and Western subjects.[12] Similar ceftaroline exposures are therefore expected in Asian and Western subjects with the same body weight receiving the same ceftaroline fosamil dosage regimen. This is in agreement with the classification of ceftaroline fosamil as a drug (similar to other cephalosporins) that is not sensitive to ethnicity according to ICH E5,[30] and the finding of the study in healthy volunteers that the PK profiles of ceftaroline and ceftaroline fosamil were similar in Chinese and Western subjects.[12]

PTA simulations were conducted using the covariate distributions from all patients in the Asia CAP study to confirm that current ceftaroline fosamil dosing regimens provide adequate PTA in an Asian patient population with CAP. High PTAs across all PK/PD targets were predicted for Asian patients with CAP treated with ceftaroline fosamil; PTAs for ceftaroline ranged from 90-100% for *S. pneumoniae, S. aureus*, and ESBL-negative *E. coli* or *K. pneumoniae* isolates, typically covering ceftaroline MIC_{90} values observed in Asia-Pacific surveillance studies between 2012-2014 for *S. pneumoniae* (0.06 to 1 mg/L for PSSP, PISP, and PRSP) and *S. aureus* (2 mg/L) and between 2013-2014 for ESBL-negative *E. coli* and *K. pneumoniae* (≤0.5 mg/L). Greater than 90% PTAs were also achieved at the EUCAST and FDA/CLSI susceptibility breakpoints for *S. pneumoniae* (≤0.25 and ≤0.5 mg/L), *S. aureus* (≤1 mg/L), and *Enterobacteriaceae* (≤0.5 mg/L). Similarly, >90% PTA was also reached at the EUCAST non–species-specific PK/PD breakpoint of ≤0.5 mg/L and for *H. influenzae* EUCAST and FDA/CLSI susceptibility breakpoints (≤0.03 and ≤0.5 mg/L), with a PK/PD target of at least 70% *f*T>MIC. This has clinical implications for dosing as the analysis confirmed that the ceftaroline fosamil dosing regimens recommended for patients with normal renal function and those with mild renal impairment (600 mg q12h given as a 1-hour IV infusion) can provide high PTAs against pathogens encountered in real-world practice in the Asia-Pacific region.

Asian CAP patients with moderate renal impairment receiving ceftaroline fosamil 400 mg q12h had similar or higher PTAs compared with those with normal renal function or mild renal impairment receiving ceftaroline fosamil 600 mg q12h. This indicated that the recommended dosage adjustment for ceftaroline fosamil should result in adequate PTAs in Asian CAP patients with moderate renal impairment. Although patients with severe renal impairment (CrCL 15-30 mL/min) or ESRD (CrCL <15 mL/min) were not assessed in this analysis, the finding of similar PK between Asian and Western subjects of similar body weight suggests that the approved dosage adjustments for Western subjects with severe renal impairment (300 mg q12h) and ESRD (200 mg q12h) can also apply to Asian subjects.

The results presented here are to our knowledge the first PTA analyses conducted for ceftaroline fosamil specifically for an Asian patient population with CAP. A major strength of this analysis is the use of real patient data from a clinical trial of Asian patients with CAP in the population PK model. Furthermore, this analysis confirmed that high PTAs were achieved at the MIC_{90} values for contemporary pathogens obtained in comprehensive surveillance programs, including those implicated to cause CAP in Asia. High PTAs were also achieved at the highest MIC values reported for pathogens in the Asia CAP study. It should be noted that in common with similar trials, the isolation rate of viable baseline pathogens for culture and susceptibility testing was low in this phase 3 study, hence only a limited number of isolates were available for inclusion in the analyses. However, the Asia-Pacific surveillance data helps to provide assurance that the trial isolates were reflective of real-life practice in the region.

Appropriate selection of empirical treatment for CAP should be based on local bacterial etiology, which can differ in Asia compared with other regions.[31] Some epidemiological studies have suggested that *S. aureus* and Gram-negative bacteria such as *K. pneumoniae* are more commonly associated with CAP in Asia compared with the United States and Europe.[31,32] However, consistent with other geographic regions, *S. pneumoniae* was confirmed to be the most commonly identified CAP pathogen in Asia in a recent systematic review of data from this region,[31] and was also the most common pathogen identified in the ceftaroline Asia CAP study.[4] Results from the Asia CAP study suggested that ceftaroline fosamil should be regarded as an alternative to ceftriaxone in empirical treatment regimens in this patient population.[4] Consistent with this finding, the results presented here confirm that treatment with ceftaroline fosamil provided high PTAs against these pathogens in Asian patients with CAP. Thus, the high PTAs reported in this analysis further support for using the ceftaroline fosamil dosing regimens (adjusted for renal function) approved in Europe and the United States, which have also shown clinical efficacy in the phase 3 Asia CAP study[4] for the treatment of Asian patients with CAP.

Conclusions

The findings from this population PK model analysis indicate that ceftaroline exhibits similar PK in Asian and Western populations. For *S. pneumoniae*, *S. aureus*, and *Enterobacteriaceae*, high PTAs (90-100%) were achieved for Asian patients with CAP treated with ceftaroline fosamil, which covered the ceftaroline MIC_{90}s recorded in recent surveillance studies of these pathogens in the Asia-Pacific region. High PTAs were also achieved at the ceftaroline EUCAST and FDA clinical breakpoints for these pathogens. These results provide further support for the use of the ceftaroline fosamil dosing regimens approved in Europe and the United States to treat Asian patients with CAP.

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Figure 1. Population Pharmacokinetic Model Diagnostic Plots for the Final Model, for All Subjects in the Western and Asian Datasets Combined

Panels show observed ceftaroline concentrations versus individual predicted ceftaroline concentrations (IPRED), observed ceftaroline concentrations versus population predicted ceftaroline concentrations (PRED), individual weighted residual error (IWRES) versus IPRED and conditional weighted residual error (CWRES) versus PRED on a semi-logarithmic scale for the final model, IWRES versus TIME and IWRES versus time after last dose (TAD) on a linear scale. Individual data points are indicated by gray circles and the points for each individual are connected with a line. The red lines represent a smooth, the horizontal black line in the lower panels is the zero line, and the diagonal black line in the upper panels is the line of identity.

Figure 2. Prediction Corrected Visual Predictive Check (pcVPC) for Ceftaroline Using the Final Model Based on 1000 Simulated Datasets for All Subjects in the Western and Asian Datasets Combined

Data points represent the observed data. Red lines are the 5th, 50th (solid), and 95th percentile based on the observed ceftaroline data. The shaded areas are 95% confidence intervals for the 5th, 50th (red), and 95th percentile prediction intervals based on the simulated data.

Figure 3. PTA for Asian CAP Patients With Normal Renal Function After Administration of Ceftaroline Fosamil 600 mg q12h as a 1-Hour Infusion, With PTA Plotted as a Function of Ceftaroline MIC Overlaid With Ceftaroline MIC Values for 448 *S. pneumoniae* Isolates Obtained During the 2014 AWARE Surveillance Program in the Asia-Pacific Region

CAP, community-acquired pneumonia; MIC, minimum inhibitory concentration; PISP, penicillin-intermediate *S. pneumoniae* (penicillin MIC of 4 mg/L); PRSP, penicillin-resistant *S. pneumoniae* (penicillin MIC of ≥8 mg/L); PSSP, penicillin-susceptible *S. pneumoniae* (penicillin MIC of ≤2 mg/L); PTA, probability of PK/PD target attainment; q12h, every 12 hours.

The values above the bars are the numbers of isolates tested at each MIC.

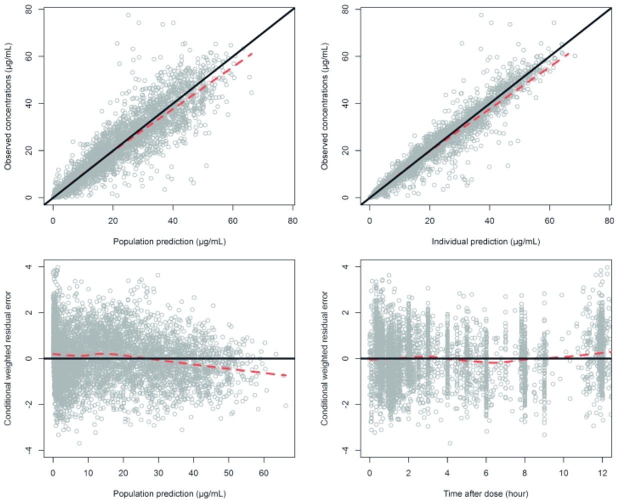
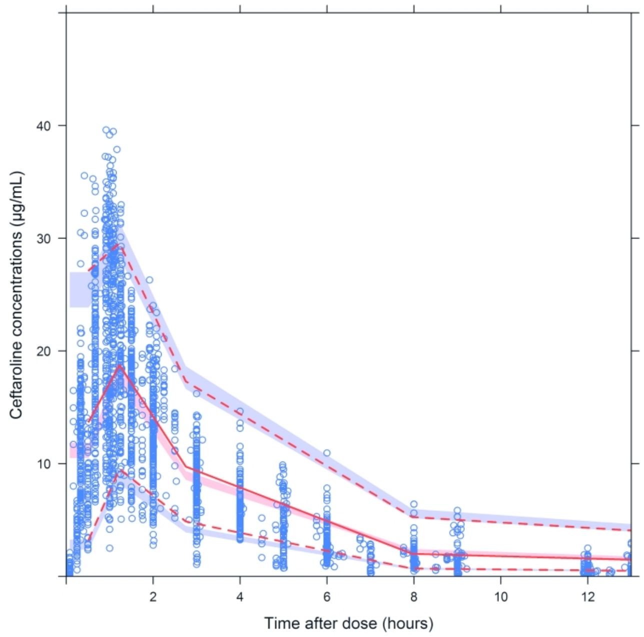


Figure 1. Population Pharmacokinetic Model Diagnostic Plots for the Final Model, for All Subjects in the Western and Asian Datasets Combined

Panels show observed ceftaroline concentrations versus individual predicted ceftaroline concentrations (IPRED), observed ceftaroline concentrations versus population predicted ceftaroline concentrations (PRED), individual weighted residual error (IWRES) versus IPRED and conditional weighted residual error (CWRES) versus PRED on a semi-logarithmic scale for the final model, IWRES versus TIME and IWRES versus time after last dose (TAD) on a linear scale. Individual data points are indicated by gray circles and the points for each individual are connected with a line. The red lines represent a smooth, the horizontal black line in the lower panels is the zero line, and the diagonal black line in the upper panels is the line of identity.



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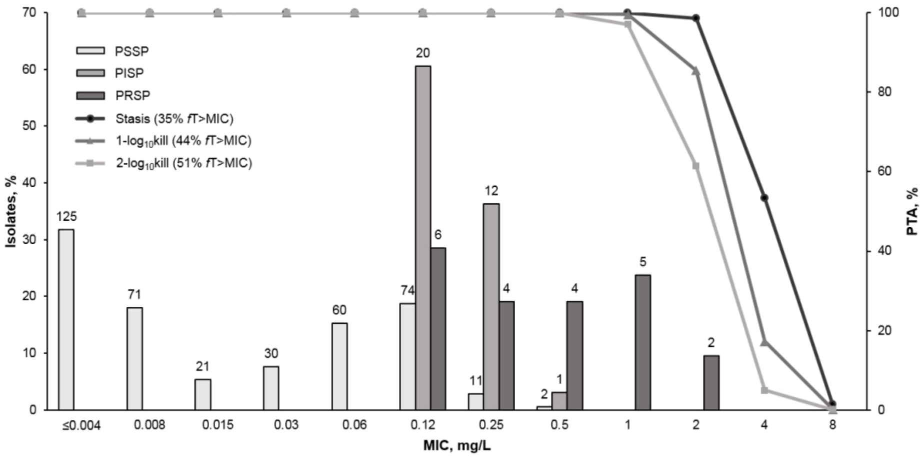
Data points represent the observed data. Red lines are the 5th, 50th (solid), and 95th percentile based on the observed ceftaroline data. The shaded areas are 95% confidence intervals for the 5th, 50th (red), and 95th percentile prediction intervals based on the simulated data.



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CAP, community-acquired pneumonia; MIC, minimum inhibitory concentration; PISP, penicillin-intermediate S. pneumoniae (penicillin MIC of 4 mg/L); PRSP, penicillin-resistant S. pneumoniae (penicillin MIC of ≥8 mg/L); PSSP, penicillin-susceptible S. pneumoniae (penicillin MIC of ≤2 mg/L); PTA, probability of PK/PD target attainment; q12h, every 12 hours.

The values above the bars are the numbers of isolates tested at each MIC.

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Table 1. Typical Parameter Estimates for the Final Ceftaroline and Ceftaroline Fosamil Population PK Model

	Value	RSE (%)
Clearance of CPT-F (CL_{cf}), L/h	234 (fixed)	NA
Central volume of distribution of CPT-F (Vc_{cf}), L	8.25 (fixed)	NA
Intercompartmental clearance of CPT-F (Q_{cf}), L/h	17.1 (fixed)	NA
Peripheral volume of distribution of CPT-F (Vp_{cf}), L	5.91 (fixed)	NA
Absorption rate for CPT-F intra-muscular administration[a] (Ka_{cf}), h^{-1}	0.528 (fixed)	NA
Clearance of CPT (CL_c), L/h	8.21	2.07
Central volume of distribution of CPT (Vc_c), L	10.3	2.75
Intercompartmental clearance of CPT (Q_c), L/h	7.75	2.12
Peripheral volume of distribution of CPT (Vp_c), L	9.15	1.17
CL_c, dialysis, L/h	10.8	1.95
Age on CL_c: $\times$ (age/36)$^\theta$	–0.264	9.14
ESRD on CL_c: $\times\ \theta$	0.339	13.1
NCrCL on CL_c: $\times$ (CrCL/80)$^\theta$ if not dialysis and NCrCL <80 mL/min	0.524	5.52
Patient on CL_c: $\times\ \theta$	1.26	2.52
Patient on Vc_c: $\times\ \theta$	1.59	3.09
IIV CL_{cf}, CV	0.447	(FIX)
IIV Vc_{cf}, CV	1.01	(FIX)
IIV Ka_{cf}, CV	0.329	(FIX)
IIV CL_c, CV	0.211	3.09
IIV Vc_c, CV	0.279	4.96
IIV Vc_c:CL_c, Correlation[b]	0.571	5.77
IIV Vp_c	0.103	10.1
IIV on proportional residual error$_c$	0.462	3.37
Proportional residual error$_{cf}$	0.362	(FIX)
Additive residual error$_{cf}$	0.0283	(FIX)
Proportional residual error$_c$	0.151	2.43
Additive residual error$_c$	0.0553	2.56

CPT, ceftaroline (when used as subscript designated c); CPT-F, ceftaroline fosamil (when used as subscript designated cf); ESRD, end-stage renal disease; NCrCL, normalized creatinine clearance; PK, pharmacokinetic; RSE, relative standard error; θ, covariate model parameter; NA, not available due to being fixed for the final model.

[a]Ceftaroline fosamil was given by intra-muscular administration in one of the studies included in the model.[21]

[b]RSE for the correlation is 0.5 x (SE_{Cov}/Covariance)

Table 2. Individual Predicted Ceftaroline Pharmacokinetic Parameters by Ceftaroline Fosamil Dosing Regimen for Subjects in the Phase 1 Study in Chinese Healthy Volunteers and the Phase 3 Asia CAP Study by dosing regimen

Study/Dosing Regimen	$C_{max,ss}$ (µg/mL)	AUC_{ss} (µg·h/mL)	$T_{1/2}$ (h)
Phase 1, ceftaroline fosamil 600 mg q12h, 1-hour infusion (n = 11)			
Geometric mean (CV)	29.7 (13.6)	66.1 (15.0)	2.13 (7.50)
Mean (SD)	29.9 (4.25)	66.8 (10.6)	2.14 (0.161)
Phase 1, ceftaroline fosamil 600 mg q8h, 2-hour infusion (n = 14)			
Geometric mean (CV)	22.0 (8.31)	67.3 (8.87)	2.02 (8.19)
Mean (SD)	22.0 (1.84)	67.6 (6.21)	2.02 (0.160)
Phase 3, ceftaroline fosamil 600 mg q12h, 1-hour infusion (n = 62)			
Geometric mean (CV)	22.2 (19.1)	64.9 (27.1)	2.41 (20.0)
Mean (SD)	22.5 (4.20)	67.3 (19.2)	2.46 (0.521)
Phase 3, ceftaroline fosamil 400 mg q12h, 1-hour infusion (n = 24)[a]			
Geometric mean (CV)	17.3 (22.3)	62.2 (20.1)	3.08 (15.1)
Mean (SD)	17.7 (3.76)	63.4 (12.1)	3.11 (0.566)

AUC_{ss}, area under the concentration-time curve at steady state; CAP, community-acquired pneumonia; $C_{max,ss}$, maximum concentration at steady state; CrCL, creatinine clearance; q8h, every 8 hours; q12h, every 12 hours; $T_{1/2}$, terminal half-life.

[a]Patients with moderate renal impairment (CrCL >30-50 mL/min) in the Asia CAP study received ceftaroline fosamil 400 mg q12h as a 1-hour infusion.[4]

Table 3. PTA Based on 5000 Simulated Asian CAP Patients With Normal Renal Function Achieving PK/PD Targets for *S. pneumoniae*, *S. aureus*, and *Enterobacteriaceae* by Ceftaroline MIC After Administration of Ceftaroline Fosamil 600 mg, as a 1-Hour Intravenous Infusion, q12h

	PTA (%)							
	S. pneumoniae			*S. aureus*			*Enterobacteriaceae*	
Ceftaroline MIC (mg/L)	Stasis (35% *f*T>MIC)	1-log_{10} kill (44% *f*T>MIC)	2-log_{10} kill (51% *f*T>MIC)	Stasis (27% *f*T>MIC)	1-log_{10} kill (31% *f*T>MIC)	2-log_{10} kill (35% *f*T>MIC)	Stasis (48.5% *f*T>MIC)	1-log_{10} kill (73% *f*T>MIC)
0.125	100	100	100	100	100	100	100	99.9
0.25	100	100	100	100	100	100	100	99.1
0.5	100	100	99.9	100	100	100	100	90.5
1	100	99.6	97.1	100	100	100	98.7	50.5
2	98.6	85.5	61.4	100	99.5	98.6	70.5	6.50
4	53.4	17.2	4.92	86.3	69.7	53.4	7.7	0.06
8	1.36	0.12	0.04	7.60	2.74	1.36	0.04	0.00

CAP, community-acquired pneumonia; MIC, minimum inhibitory concentration; PD, pharmacodynamic; PK, pharmacokinetic; PTA, probability of PK/PD target attainment; q12h, every 12 hours.

Table 4. PTA Based on 5000 Simulated Asian CAP Patients With Normal Renal Function Achieving PK/PD Targets for *S. pneumoniae*, *S. aureus*, and *Enterobacteriaceae* at Ceftaroline MIC_{90}s (Based on Isolates Obtained From the Asia-Pacific Region in 2012, 2013, and 2014 From the AWARE Ceftaroline Surveillance Studies) After Administration of Ceftaroline Fosamil 600 mg as a 1-Hour Intravenous Infusion, q12h

	2012 Surveillance[a]				2013 Surveillance[b]				2014 Surveillance[c]			
		PTA (%)				PTA (%)				PTA (%)		
Pathogen	MIC_{90} (mg/L)	Stasis	1-log_{10} kill	2-log_{10} kill	MIC_{90} (mg/L)	Stasis	1-log_{10} kill	2-log_{10} kill	MIC_{90} (mg/L)	Stasis	1-log_{10} kill	2-log_{10} kill
S. pneumoniae												
PSSP	0.06	100	100	100	0.12	100	100	100	0.12	100	100	100
PISP	0.25	100	100	100	0.25	100	100	100	0.25	100	100	100
PRSP	0.5	100	100	99.9	0.5	100	100	99.9	1	100	99.6	97.1
S. aureus												
All	2	100	99.5	98.6	2	100	99.5	98.6	2	100	99.5	98.6
MSSA	0.25	100	100	100	0.25	100	100	100	0.25	100	100	100
Enterobacteriaceae												
All *E. coli*	>128	0	0	ND	>128	0	0	ND	>128	0	0	ND
ESBL-negative *E. coli*[d]	NR	ND	ND	ND	0.5	100	90.5	ND	0.5	100	90.5	ND
All *K. pneumoniae*	>128	0	0	ND	>128	0	0	ND	>128	0	0	ND
ESBL-negative *K. pneumoniae*[d]	NR	ND	ND	ND	0.25	100	99.1	ND	0.25	100	99.1	ND

CAP, community-acquired pneumonia; MIC, minimum inhibitory concentration; ND, not determined; NR, not reported (specific data not collected on ESBL-negative pathogens); PD, pharmacodynamic; PK, pharmacokinetic; PTA, probability of PK/PD target attainment; MSSA, methicillin-susceptible *S. aureus*; PISP, penicillin-intermediate *S. pneumoniae*; PRSP, penicillin-resistant *S. pneumoniae;* PSSP, penicillin-susceptible *S. pneumoniae;* q12h, every 12 hours.

[a]Based on 406 *S. pneumoniae* (310 PSSP, 81 PISP, and 15 PRSP), 532 *K. pneumoniae*, and 779 *E. coli* isolates collected in the 2012 AWARE surveillance study. [b]Based on 530 *S. pneumoniae* (406 PSSP, 96 PISP, and 28 PRSP), 2595 *S. aureus* (1021 MSSA), 718 *K. pneumoniae* (472 ESBL-negative), and 1017 *E. coli* (639 ESBL-negative) isolates collected in the 2013 AWARE surveillance study.

[c]Based on 448 *S. pneumoniae* (394 PSSP, 33 PISP, and 21 PRSP), 1640 *S. aureus* (622 MSSA), 639 *K. pneumoniae* (412 ESBL-negative), and 700 *E. coli* (439 ESBL-negative) isolates collected in the 2014 AWARE surveillance study.

[d]A ceftazidime or aztreonam MIC >1 mg/L was used as a phenotypic marker to define ESBL-positive isolates.

Table 5. PTA Based on 5000 Simulated Asian CAP Patients With Normal Renal Function Achieving Species-Specific and Non–species-specific PK/PD Targets at EUCAST and FDA/CLSI Breakpoints After Administration of Ceftaroline Fosamil 600 mg, as a 1-hour Infusion q12h

Pathogen	Susceptible MIC Breakpoint (mg/L)	PTA (%)		
		Stasis	1-$\log_{10}$ kill	2-$\log_{10}$ kill
S. pneumoniae	≤0.5[a]	100	100	99.9
	≤0.25[b]	100	100	100
S. aureus	≤1[a,b]	100	100	100
Enterobacteriaceae	≤0.5[a,b]	100	90.5	ND
H. influenzae	≤0.5[a]	>90% at a PK/PD target of ≥70% *f*T>MIC		
	≤0.03[b]	100% at a PK/PD target of 100% *f*T>MIC		
Non–species-specific	≤0.5[b]	>90% at a PK/PD target of ≥70% *f*T>MIC		

CAP, community-acquired pneumonia; MIC, minimum inhibitory concentration; ND, not determined; PD, pharmacodynamic; PK, pharmacokinetic; PTA, probability of PK/PD target attainment; q12h, every 12 hours.

[a]FDA/CLSI breakpoint.

[b]EUCAST breakpoint.

Supplementary Material

Population Pharmacokinetic Modeling and Probability of Target Attainment Analyses in Asian Patients With Community-Acquired Pneumonia Treated With Ceftaroline Fosamil

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Bioanalytical Methods

Ceftaroline fosamil, ceftaroline and ceftaroline M-1 concentrations in plasma samples were determined using validated liquid chromatography coupled with tandem mass spectrometry (LC–MS/MS; Covance Bioanalytical Services LLC, Indianapolis, IN, USA) methods in each study, with the exception of study P903-17, which used a validated high-performance liquid chromatography (HPLC)-ultraviolet detection method. Plasma samples (50 µL) were combined with equal amounts of the corresponding stable isotope labelled internal standards (ceftaroline fosamil-d3, ceftaroline-d3, or ceftaroline M-1-d3), and chilled methanol was subsequently added to induce protein-precipitation. The resulting supernatants were evaporated to dryness, reconstituted with 20 mM ammonium formate and chromatographic separation was achieved using a Waters Atlantis dC_{18} column (150 by 2.1 mm, 5 µm particle size) with a gradient mobile phase consisting of ammonium formate, isopropyl alcohol, methanol, water, and a flow rate of 0.6 ml/min. Analytes were detected by electrospray ionisation (ESI) mass spectrometry with multiple-reaction monitoring (MRM) of positive ions. The MRM in positive ion mode used precursor→product ions of *m/z* 685.0→208.0, *m/z* 605.0→209.0, *m/z* 623.1→209.0, *m/z* 688.0→211.0, *m/z* 608.1→212.0, and *m/z* 626.1→212.0 to monitor ceftaroline fosamil, ceftaroline, ceftaroline M-1, and their internal standards, ceftaroline fosamil-d3, ceftaroline-d3, or ceftaroline M-1-d3. Quantification was directly determined from the ratio of the analyte peak area to their respective stable isotope labelled internal standard compound. The lower limit of quantification for all analytes (LLOQ) was 0.05 µg/mL in each study, with the exception of studies P903-1, P903-2 and P903-3, which used a LLOQ of 0.01 µg/mL. At the LLOQ, intra-day accuracy (percent bias) and intra-day precision (% coefficient of variation) were within the ranges of ±6.2% to ±8.4% and ≤6.1% to ≤6.8%, respectively. Inter-day accuracy and inter-day precision at the LLOQ ranged from ±4.3% to ±8.7% and ≤5.9% to ≤6.5%, respectively.

Table S1 Summary of Studies Included in the Analysis Dataset for the Final Model

Name/Study protocol number (clinicaltrials.gov registration, if available)	**Description**	**LLOQ in plasma**
Phase 1		
CXL-PK-01[1]	A phase 1 study of single and multiple intravenous doses of ceftaroline fosamil and avibactam in healthy subjects	0.05 µg/mL
P903-01[2]	A phase 1, randomized, double-blind, placebo controlled, 2 part, single and multiple ascending dose study of ceftaroline fosamil in healthy adults	0.01 µg/mL.
P903-02[2]	A phase 1 open-label study of single intravenous doses of ceftaroline fosamil in subjects with normal renal function, mild renal impairment, or moderate renal impairment	0.01 µg/mL
P903-04[2]	An open-label pharmacokinetic, safety, and tolerability study of single intravenous doses of ceftaroline fosamil in subjects with normal renal function or severe renal impairment	0.05 µg/mL
P903-11[2]	An open-label pharmacokinetic, safety, and tolerability study of single intravenous doses of ceftaroline in healthy elderly and healthy young adult subjects	0.05 µg/mL
P903-13[2]	A single-dose, open-label study to assess the metabolism, elimination and safety of ceftaroline prodrug after intravenous administration of [^{14}C] ceftaroline fosamil in healthy subjects	0.05 µg/mL
P903-14[3]	A phase 1, multiple-dose, open-label study to assess the effect of ceftaroline on the intestinal microflora of healthy human subjects	0.05 µg/mL
P903-15 (NCT00633126)[4]	Pharmacokinetics of a single dose of ceftaroline in subjects 12 to 17 years of age receiving empiric parenteral antibiotic therapy for suspected infections	0.05 µg/mL
P903-17[5]	A phase 1, two-part, single- and multiple-dose study to determine the safety, tolerability and	0.05 µg/mL

	pharmacokinetics of ceftaroline fosamil administered by intramuscular injection in healthy subjects	
P903-18[2]	An open-label pharmacokinetic, safety, and tolerability study of single intravenous doses of ceftaroline fosamil in subjects with end-stage renal disease (ESRD) on intermittent haemodialysis and subjects with normal renal function	0.05 μg/mL
P903-20 (data on file)	A phase 1, randomized, double-blind, placebo-controlled study to determine the safety and pharmacokinetics of single doses (Part A) and multiple-dose regimens (Part B) of ceftaroline in healthy subjects	0.05 μg/mL
D3720C00005 (NCT01458743)[6]	**A phase 1 open-label study to assess the safety and pharmacokinetics of ceftaroline in healthy Chinese volunteers following single and multiple administration of 600 mg ceftaroline fosamil as 60-minute intravenous infusion every 12 hours and as 120-minute intravenous infusion every 8 hours**	0.05 μg/mL
Phase 2		
P903-03[7]	A phase 2, multicenter, randomized, observer-blinded study to evaluate the safety and efficacy of ceftaroline fosamil versus standard therapy in adult subjects with complicated skin and skin structure infections	0.01 μg/mL
Phase 3		
CANVAS 1/P903-06 (NCT00424190)[8]	A phase 3, multicenter, randomized, double-blind, comparative study to evaluate the safety and efficacy of ceftaroline versus vancomycin plus aztreonam in adult subjects with complicated skin and skin structure infection	0.05 μg/mL
CANVAS 2/P903-07 (NCT00423657)[9]	A phase 3, multicenter, randomized, double-blind, comparative study to evaluate the safety and efficacy of ceftaroline versus vancomycin plus aztreonam in adult subjects with complicated skin and skin structure infection	0.05 μg/mL

FOCUS 1/P903-08 (NCT00621504)[10]	A phase 3, multicenter, randomized, double-blind, comparative study to evaluate the safety and efficacy of ceftaroline versus ceftriaxone, with adjunctive clarithromycin, in the treatment of adult subjects with community-acquired pneumonia	0.05 µg/mL
FOCUS 2/P903-09 (NCT00509106)[11]	A phase 3, multicenter, randomized, double-blind, comparative study to evaluate the safety and efficacy of ceftaroline versus ceftriaxone in the treatment of adult subjects with community-acquired pneumonia	0.05 µg/mL
Asia CAP/D3720C00002 (NCT01371838)[12]	**A phase 3, multicentre, randomized, double-blind, comparative study to evaluate the efficacy and safety of intravenous ceftaroline fosamil versus intravenous ceftriaxone in the treatment of adult hospitalized patients with community-acquired bacterial pneumonia in Asia**	0.05 µg/mL

Studies in Asian patients indicated with bold font. Validated LC-MS/MS methods were used to determine plasma concentrations of ceftaroline and ceftaroline fosamil in each study apart from study P903-17, which used a validated HPLC method.[13]

Table S2. Summary of Baseline Covariates Included in the Analysis Dataset for the Final Population PK Model

	Western Dataset N = 421	New Asian Studies N = 112	All Data N = 533
Age (years)	42 (12, 88)	65 (19, 93)	47 (12, 93)
Body weight (kg)	74 (40, 134)	62 (45, 86)	72 (40, 134)
BMI (kg/m^2)	24.6 (17.5, 38.2)	22.6 (15.6, 30.4)	24.2 (15.6, 38.2)
BSA (m^2)	1.90 (1.28, 2.58)	1.66 (1.37, 2.00)	1.84 (1.28, 2.58)
BSA normalized CrCL (mL/min)/(1.73 m^2)	93.0 (8.2, 268.6)	81.2 (35.9, 156.1)	92.0 (8.2, 268.6)
Height (cm)	174 (147, 195)	165 (141, 178)	172 (141, 195)
Dialysis status			
No dialysis	415 (99%)	112 (100%)	527 (99%)
ESRD	6 (1%)	0 (0%)	6 (1%)
Dialysis	0 (0%)	0 (0%)	0 (0%)
Renal function			
Normal (CrCL >80 mL/min)	266 (63%)	54 (48%)	320 (60%)
Mild renal impairment (CrCL >50-80 mL/min)	107 (25%)	39 (35%)	146 (27%)
Moderate renal impairment (CrCL >30-50 mL/min)	33 (8%)	19 (17%)	52 (10%)
Severe renal impairment (CrCL 15-30 mL/min)	9 (2%)	0 (0%)	9 (2%)
ESRD or dialysis (CrCL <15 mL/min)	6 (1%)	0 (0%)	6 (1%)
Patient status			
Healthy volunteer	195 (46%)	26 (23%)	221 (41%)
Patient	226 (54%)	86 (77%)	312 (59%)
Race			
Caucasian	306 (73%)	0 (0%)	306 (57%)
Black	54 (13%)	0 (0%)	54 (10%)
Asian[a]	11 (3%)	112 (100%)	123 (23%)
Other	50 (12%)	0 (0%)	50 (9%)
Sex			
Male	271 (64%)	77 (69%)	348 (65%)
Female	150 (36%)	35 (31%)	185 (35%)

BMI, body mass index; BSA, body surface area; CrCL, creatinine clearance; ESRD, end-stage renal disease.

Data presented as median (min, max) or n (%).

[a]Asian includes Indians.

Table S3. PTA Based on 5000 Simulated Asian Patients With CAP Achieving Non–Species-Specific %*f*T>MIC PK/PD Targets at Steady State by Ceftaroline MIC Value After Administration of Ceftaroline Fosamil 600 mg as a 1-Hour Intravenous Infusion, q12h

	PTA, %						
Ceftaroline MIC (mg/L)	*f*T>MIC = 20%	*f*T>MIC = 30%	*f*T>MIC = 40%	*f*T>MIC = 50%	*f*T>MIC = 60%	*f*T>MIC = 70%	*f*T>MIC = 80%
0.125[a]	100	100	100	100	100	100	99.8
0.25	100	100	100	100	100	99.6	96.9
0.5	100	100	100	100	99.2	94.3	78.3
1	100	100	99.9	98.2	86.7	60.2	31.1
2	100	99.7	94.1	67.4	31.1	9.76	2.62
4	99.4	76.9	30.7	6.72	1.06	0.18	0.02
8	37.7	4.20	0.26	0.04	0.00	0.00	0.00

CAP, community-acquired pneumonia; MIC, minimum inhibitory concentration; PD, pharmacodynamic; PK, pharmacokinetic; PTA, probability of PK/PD target attainment; q12h, every 12 hours.

[a]MICs <0.125 mg/L have 100% PTA for all PK/PD targets.

Table S4. PTA Based on 5000 Simulated Asian CAP Patients With Mild Renal Impairment Achieving PK/PD Targets for *S. pneumoniae, S. aureus*, and *Enterobacteriaceae* by Ceftaroline MIC After Administration of 600 mg Ceftaroline Fosamil as a 1-Hour Intravenous Infusion, q12h

	PTA, %							
Ceftaroline MIC (mg/L)	***S. pneumoniae***			***S. aureus***			***Enterobacteriaceae***	
	Stasis (35% *f*T>MIC)	1-$\log_{10}$ kill (44% *f*T>MIC)	2-$\log_{10}$ kill (51% *f*T>MIC)	Stasis (27% *f*T>MIC)	1-$\log_{10}$ kill (31% *f*T>MIC)	2-$\log_{10}$ kill (35% *f*T>MIC)	Stasis (48.5% *f*T>MIC)	1-$\log_{10}$ kill (73% *f*T>MIC)
0.125	100	100	100	100	100	100	100	99.9
0.25	100	100	100	100	100	100	100	99.9
0.5	100	100	100	100	100	100	100	97.7
1	100	100	99.6	100	100	100	99.8	79.0
2	99.8	96.4	86.0	100	100	99.8	90.7	27.2
4	80.3	45.8	22.6	96.3	89.2	80.3	29.1	1.26
8	7.10	1.34	0.42	25.5	13.3	7.10	0.62	0.00

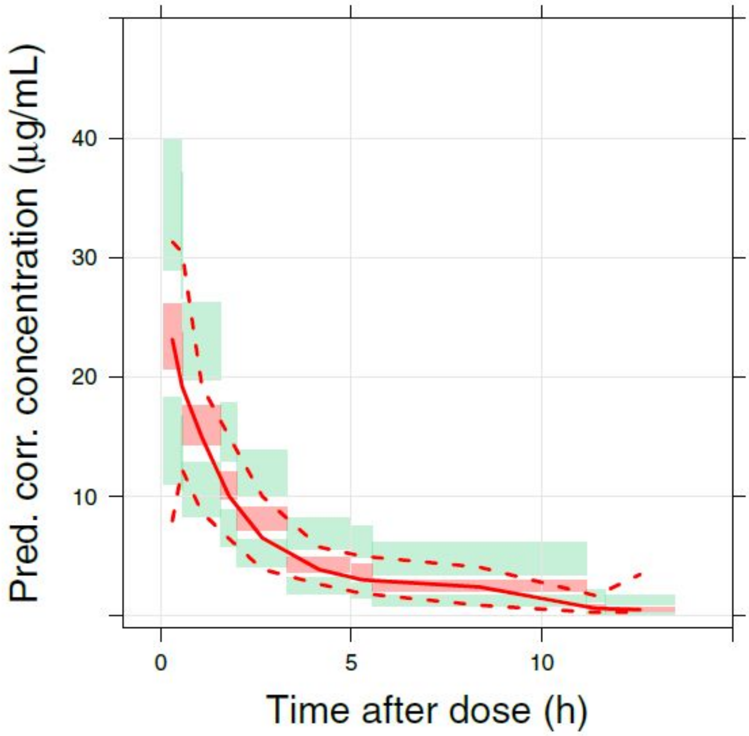
CAP, community-acquired pneumonia; MIC, minimum inhibitory concentration; PD, pharmacodynamic; PK, pharmacokinetic; PTA, probability of PK/PD target attainment; q12h, every 12 hours.

Table S5. PTA for 5000 Simulated Asian CAP Patients With Moderate Renal Impairment Achieving the PK/PD Targets for *S. pneumoniae, S. aureus*, and *Enterobacteriaceae* by Ceftaroline MIC After Administration of 400 mg Ceftaroline Fosamil as 1-Hour Intravenous Infusion, q12h

	PTA, %							
	S. pneumoniae			***S. aureus***			***Enterobacteriaceae***	
Ceftaroline MIC (mg/L)	Stasis (35% *f*T>MIC)	1-$\log_{10}$ kill (44% *f*T>MIC)	2-$\log_{10}$ kill (51% *f*T>MIC)	Stasis (27% *f*T>MIC)	1-$\log_{10}$ kill (31% *f*T>MIC)	2-$\log_{10}$ kill (35% *f*T>MIC)	Stasis (48.5% *f*T>MIC)	1-$\log_{10}$ kill (73% *f*T>MIC)
0.125	100	100	100	100	100	100	100	100
0.25	100	100	100	100	100	100	100	100
0.5	100	100	100	100	100	100	100	100
1	100	100	99.9	100	100	100	100	91.6
2	99.9	97.7	91.5	100	100	99.9	94.1	43.0
4	76.2	47.1	26.7	93.7	85.7	76.2	32.8	2.28
8	4.20	1.12	0.22	14.6	7.68	4.20	0.42	0.00

CAP, community-acquired pneumonia; MIC, minimum inhibitory concentration; PD, pharmacodynamic; PK, pharmacokinetic; PTA, probability of PK/PD target attainment; q12h, every 12 hours.

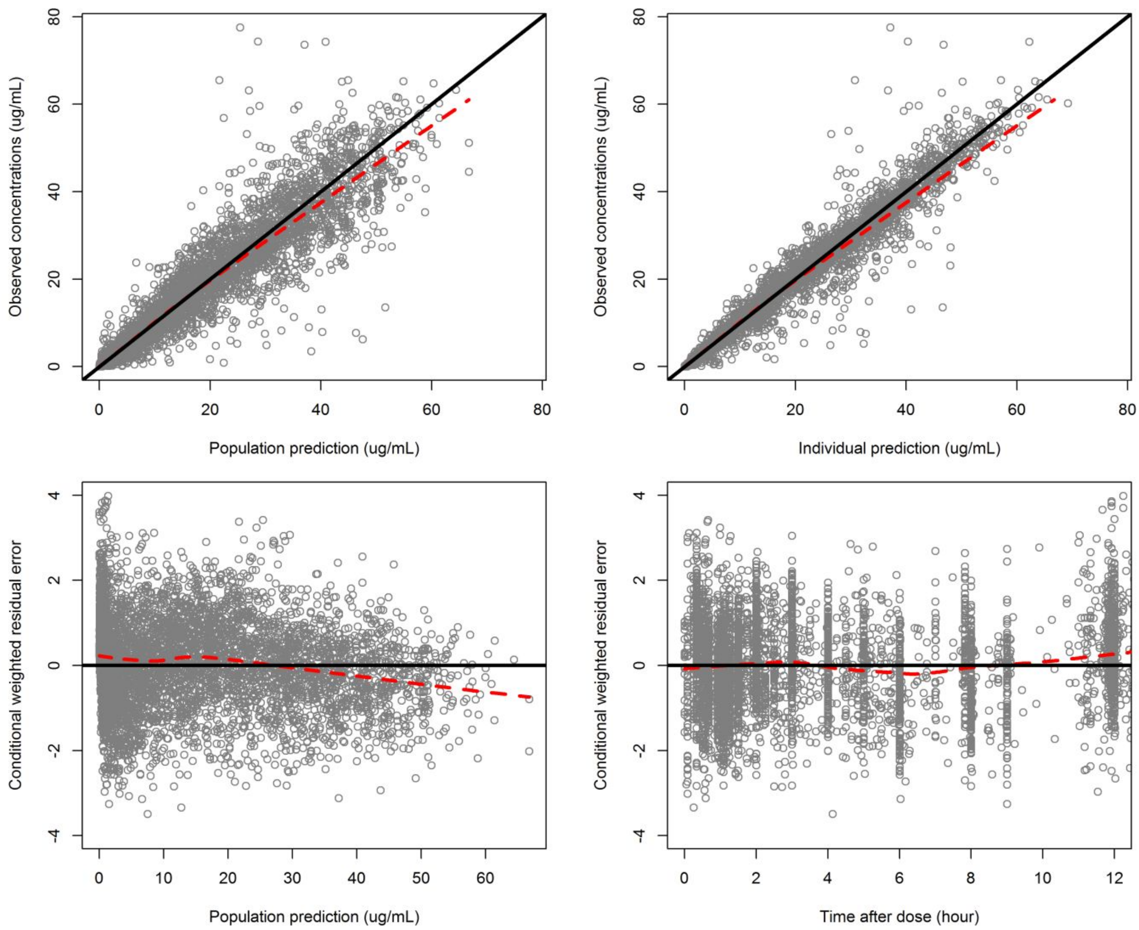
Figure S1. Prediction Corrected Visual Predictive Check for Ceftaroline Using the Final Model Based on 1000 Simulated Datasets for Patients From the Phase 3 Asia CAP Study.



CAP, community-acquired pneumonia.

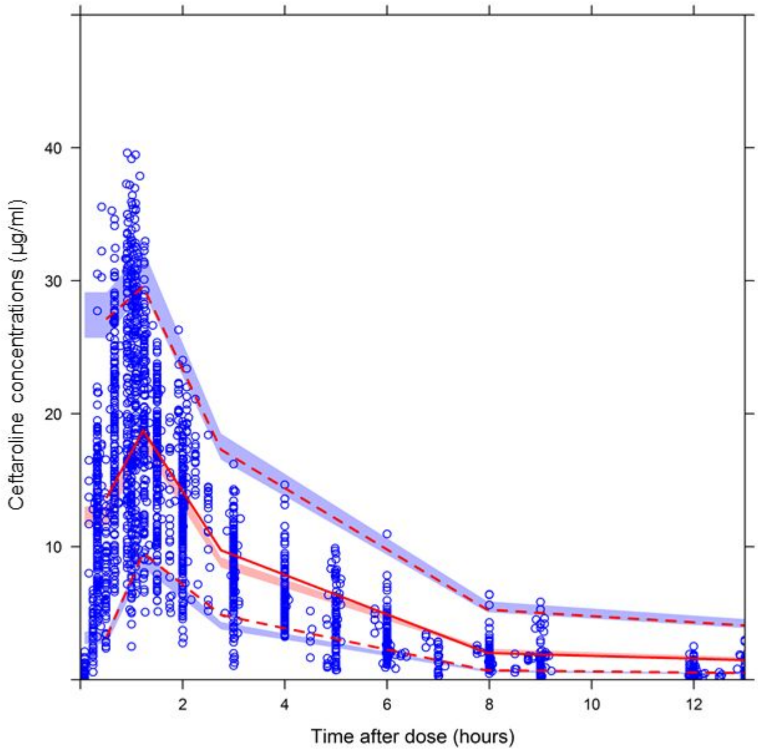
The red lines are the 5th, 50th (solid), and 95th percentile based on the observed data. The shaded areas are 95% confidence intervals for the 5th, 50th (red), and 95th percentile prediction intervals based on the simulated data.

Figure S2. Population Pharmacokinetic Model Diagnostic Plots for Ceftaroline After Reintroducing Ceftaroline Fosamil Concentrations Into the Final Model



Panels show observed ceftaroline concentrations versus individual predicted ceftaroline concentrations (IPRED), observed ceftaroline concentrations versus population predicted ceftaroline concentrations (PRED), individual weighted residual error (IWRES) versus IPRED and conditional weighted residual error (CWRES) versus PRED on a semi-logarithmic scale for the final model, IWRES versus TIME and IWRES versus time after last dose (TAD) on a linear scale. Individual data points are indicated by gray circles and the points for each individual are connected with a line. The red lines represent a smooth, the horizontal black line in the lower panels is the zero line, and the diagonal black line in the upper panels is the line of identity.

Figure S3. Prediction Corrected Visual Predictive Check for Ceftaroline After Reintroducing Ceftaroline Fosamil Concentrations Into the Final Model Based on 1000 Simulated Datasets for All Subjects in the Western and Asian Datasets Combined



Data points represent the observed data. Red lines are the 5th, 50th (solid), and 95th percentile based on the observed ceftaroline data. The shaded areas are 95% confidence intervals for the 5th, 50th (red), and 95th percentile prediction intervals based on the simulated data

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